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DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

A SIMPLE MEANS OF PREPARING QUINOXALINE DERIVATIVES: DIRECT INTRODUCTION OF C-NUCLEOPHILES INTO THE QUINOXALINE NUCLEUS BY SUBSTITUTING A HYDROGEN ATOM

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Unsubstituted quinoxaline (I) reacts with dimedone, indanedione, and 1-phenyl-3-methylpyrazol-5-one in dimethylsulfoxide in the presence of acid to form monosubstitution products II – IV. Quinoxaline reacts with 1,3-dimethylbarbituric acid in dimethylsulfoxide solution at room temperature to form monosubstitution product V without external catalysis. Heating of I with resorcinol in ethanol in the presence of acid produced resorcinol derivative VI. In the presence of base, quinoxaline reacts with 1-phenyl-3-methylpyrazol-5-one to form dipyrazolylmethane VII and tetrapyrazolylethane derivative VIII. Compound VIII undergoes cleavage to form dipyrazolylmethane VII in dimethylformamide solution with boiling or in the presence of iodine at room temperature.

Keywords: quinoxaline, reactions with nucleophiles.

Quinoxaline derivatives include compounds with different types of biological activity [1, 2]. Quinoxaline derivatives – quinoxidine and dioxidine – are used as antimicrobial substances [3]. A series of condensed quinoxalines has been patented as antitumor agents [4].

Substituted quinoxalines are synthesized either by condensation of the corresponding substituted *o*-phenylenediamines with 1,2-dihydroxy derivatives or by substitution reactions in the quinoxaline nucleus. N-alkyl quaternary quinoxaline salts react with 1,3-diketones to form di-attachment or cyclo-attachment products at the C_2-C_3 bond [5, 6]. At the same time, the literature contains virtually no data on the synthesis of products by direct insertion of CH acid residues into unsubstituted quinoxaline.

We have observed that unsubstituted quinoxaline (I) interacts with 1,3-diketones – indanedione and dimedone – in the presence of hydrochloric acid in dimethylsulfoxide at room temperature to form 2-(1,3-dihydroxyindan-2-ylidene)-1*H*-1,2-dihydroquinoxaline (II) and 2-(1,3-dihydroxy-5,5-dimethylcyclohexan-2-ylidene)-1*H*-1,2-dihydroquinoxaline (III) respectively (scheme 1). In analogous conditions, I reacts with 1-phenyl-3-methylpyrazol-5-one to yield 2-(1-phenyl-3-methyl-5-oxypyrazol-4-yliden)-1*H*-1,2-dihydroquinoxaline (IV).

It is interesting that 1,3-dimethylbarbituric acid I reacts in aqueous dimethylsulfoxide at room temperature to form 2-(1,3-dimethyl-2,4,6-trioxy-1,2,3,4,5,6-hexahydropyrimid-5-yliden)-1*H*-1,2-dihydroquinoxaline (V) in the absence of an external catalyst. We first reported this conversion in a recent letter to the editor [7].

Heating with resorcinol in boiling ethanol in the presence of hydrochloric acid converts I into 2-(2,4-dihydroxyphenyl)quinoxaline (VI).

The molecular weights of compounds II-VI measured by mass spectrometry were consistent with calculated values. A characteristic diagnostic property for monosubstitution prod-

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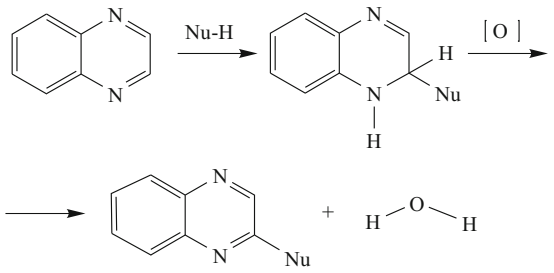
ucts II – VI in the ^{1}H NMR spectrum was the presence of individual signals from the pyrazine ring proton at 9.0 – 10.5 ppm.

It is interesting that the reaction of quinoxaline I with C nucleophiles did not stop at the stage of σ-adduct formation, but continued to oxidation of these compounds to aromatic substitution products.



In a short report, the authors of the present study recently reported unusual conversions of unsubstituted I with 1-phenyl-3-methylpyrazol-5-one in dimethylsulfoxide in the presence of base [8]. In fact, the reaction of I with 1-phenyl-3-methylpyrazol-5-one in the presence of triethylamine yielded the known dipyridylmethane (VII) [9] and 1,1,2,2-tetra(5-methyl-3-oxo-2-phenyl-1,2-dihydro-3*H*-pyrazol-4-yl)ethane (VIII). In addition, preparative thin-layer chromatography on silica gel was used to isolate *o*-phenylenediamine IX from the reaction products (scheme 2).

A singlet signal from two equivalent ethane protons in the PMR spectrum at 4.74 ppm was typical of tetrapyrazolyl derivative VIII.

The fine structure of product VIII was established by x-ray structural analysis (Fig. 1) [8].

In the conversion of I with 1-phenyl-3-methylpyrazolol-5-one in the presence of base, quinoxaline served as a two-carbon fragment donor. During the reaction, the initially forming tetrapyrazolyl derivative VIII underwent cleavage with formation of small quantities of dipyrazolylmethane VII.

It should be noted that transient heating of tetrapyrazolyl derivative VIII in boiling dimethylformamide produced dipyrazolylmethane VII. Product VIII was also converted into VII in dimethylformamide in the presence of iodine at room temperature. The conversion VIII > VII also occurred on transient heating of crystals of substance to 255 – 260°C.

Thus, these studies revealed a simple means of obtaining monosubstituted quinoxaline derivatives with formation of water during substitution of the hydrogen atom, which is of practical interest in the synthesis of new potentially biologically active derivatives. It should also be noted that the unusual conversions of quinoxaline seen in reactions with 1-phenyl-3-methylpyrazol-5-one may be of interest in studying and understanding metabolic processes involving reagents of this type.

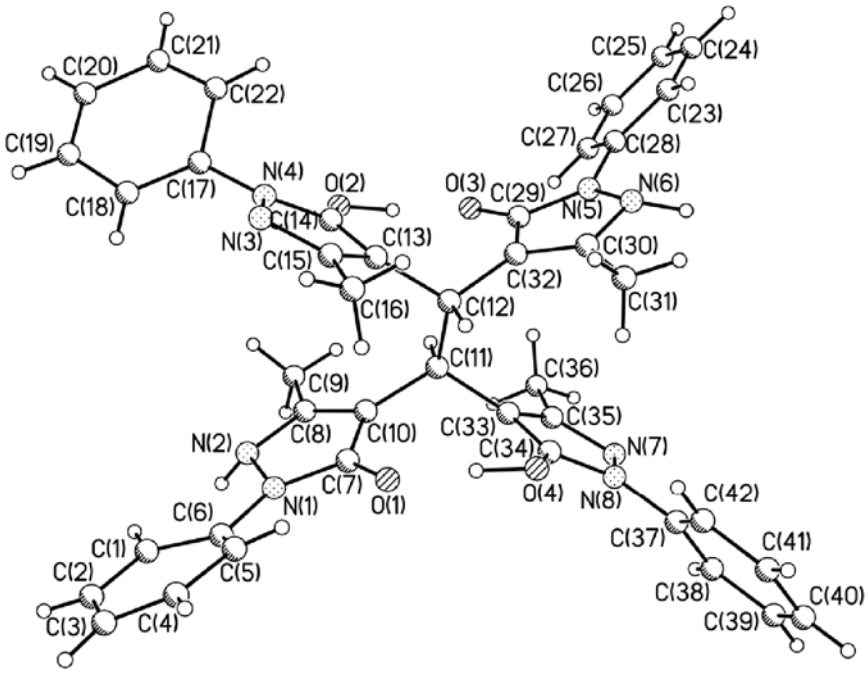
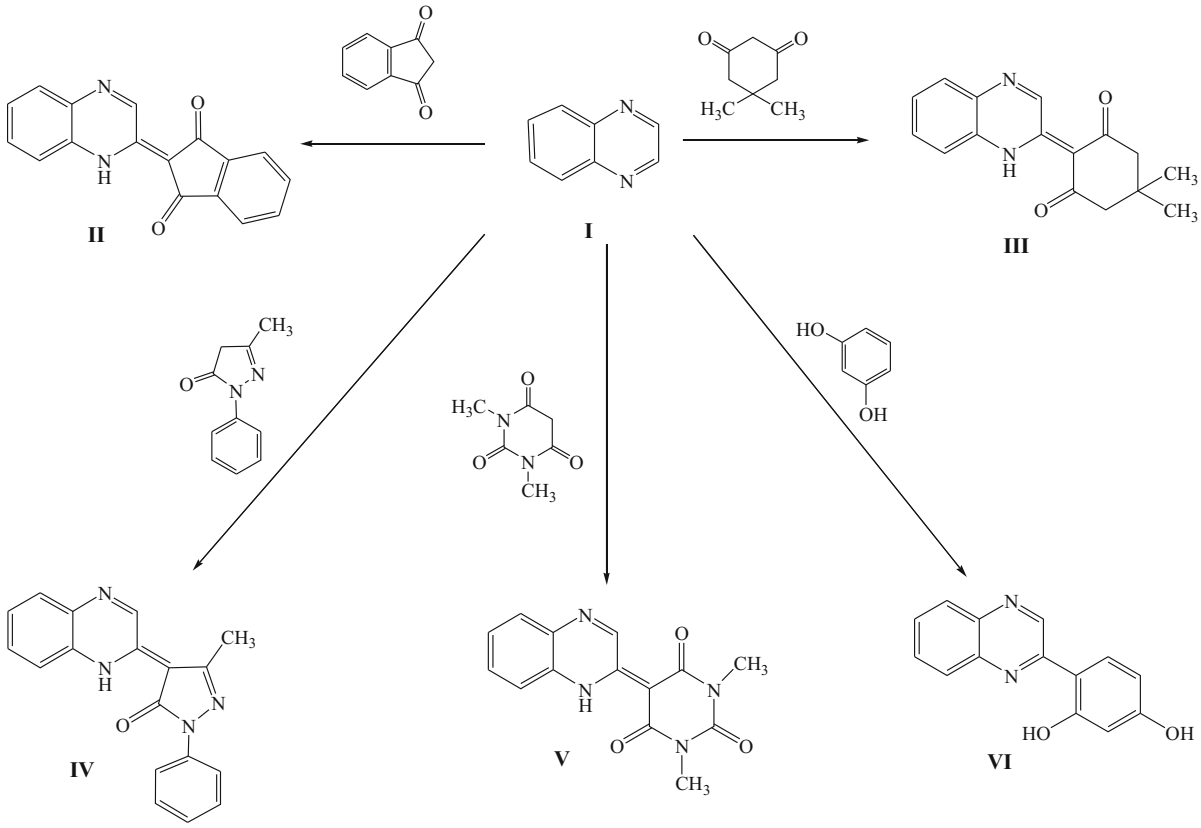


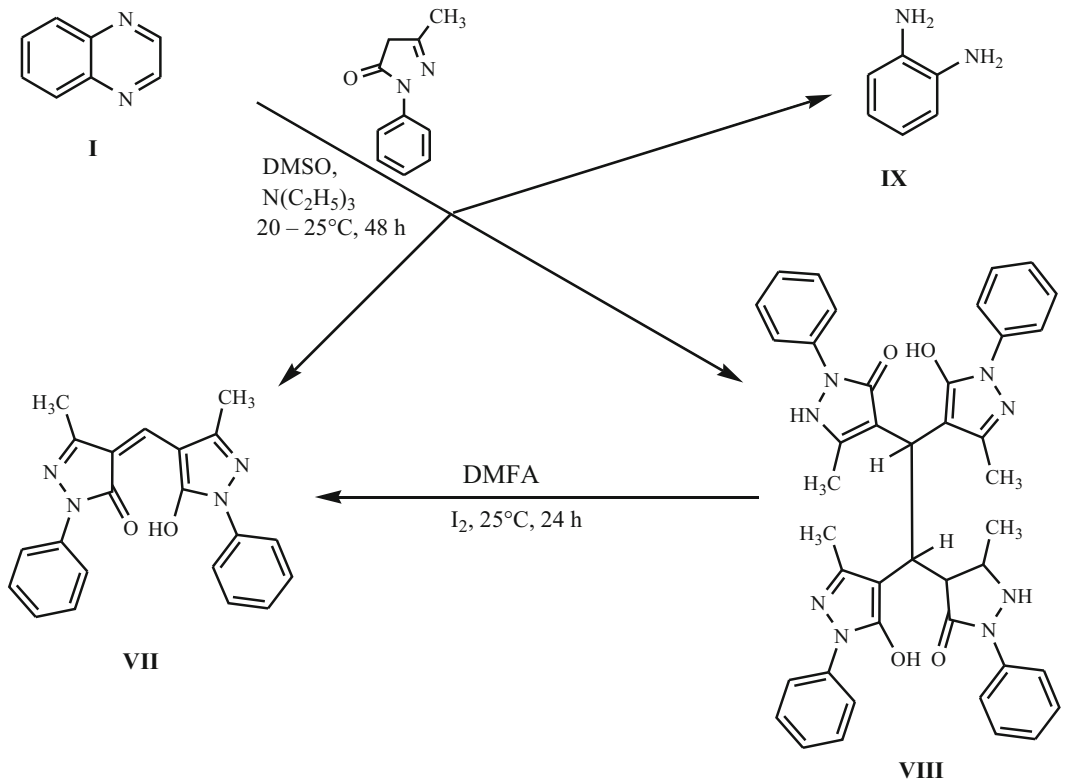
Fig. 1. Molecular structure of compound VIII.

Main bond lengths: N(1)-N(2) 1.3934(17); N(2)-C(8) 1.3617(19); C(8)-C(10) 1.358(2); C(7)-C(10) 1.428(2); N(1)-C(7) 1.3729(18); N(1)-C(6) 1.419(2); O(1)-C(7) 1.2573(17); N(5)-N(6) 1.3842(17); N(6)-C(30) 1.3680(19); C(32)-C(30) 1.356(2); C(29)-C(32) 1.422(2); C(29)-N(5) 1.3717(18); N(5)-C(28) 1.4193(19); O(3)-C(29) 1.2632(17); N(3)-N(4) 1.3794(17); N(3)-C(15) 1.3296(18); C(15)-C(13) 1.400(2); C(13)-C(14) 1.373(2); N(4)-C(14) 1.3570(19); N(4)-C(17) 1.427(2); O(2)-C(14) 1.3302(18); N(8)-N(7) 1.3817(17); N(7)-C(35) 1.3282(19); C(33)-C(35) 1.407(2); N(8)-C(34) 1.3619(18); N(8)-C(37) 1.4148(19); O(4)-C(34) 1.3374(17).

Scheme 1



Scheme 2



EXPERIMENTAL SECTION

NMR spectra were recorded on a DRX-400 spectrometer (Federal Republic of Germany). Electron impact mass spectra (MS-EI) were obtained on a MicrOTOF-Q instrument from Bruker Daltonics with a mean ionizing tension of 75 eV at a temperature of 250°C. Elemental analysis data corresponded to calculated values.

2-(1,3-Dioxoindan-2-yliden)-1*H*-1,2-dihydroquinoxaline (II). Compound I (0.065 g, 0.5 mmol) and indanedione (0.140 g, 0.98 mmol) were held for 2 h at 20 – 25°C in 2 ml of dimethylsulfoxide (DMSO) in the presence of 0.05 ml of concentrated HCl. The reaction mix was filtered and the resulting precipitate was recrystallized from ethanol. The yield was 0.055 g (40%). Melting temperature was 250°C. The PMR spectrum (DMSO-d_6), δ, ppm, was: 7.58 (t, 1H, J 8.0 Hz, $CH_{quinoxaline}$), 7.70 (s, 4H, $CH_{indanedione}$), 7.74 (t, 1H, J 8.0 Hz, $CH_{quinoxaline}$), 7.93 (s, 1H, $CH_{quinoxaline}$), 8.04 (d, 1H, J 8.0 Hz, $CH_{quinoxaline}$), 9.94 (s, 1H, $CH_{quinoxaline}$), 13.51 (broad s, 1H, OH). The mass spectrum, *m*/*z* (I_{rel}, %), was: 274 [M^+] (100). $C_{17}H_{10}N_2O_4$.

2-(1,3-Dioxo-5,5-dimethylcyclohexan-2-yliden)-1*H*-1,2-dihydroquinoxaline (III). Compound I (0.130 g, 1.0 mmol) and dimedone (0.160 g, 1.14 mmol) were held for 24 h at 20 – 25°C in 1 ml of DMSO in the presence of 0.1 ml of concentrated HCl. The reaction mixture was filtered. The precipitate of III was recrystallized form ethanol. The yield was 0.120 g (45%). The melting temperature was 173 – 174°C. The PMR spectrum (DMSO-d_6), δ, ppm, was: 1.07 (s, 6H, 2 × CH_3); 7.67 (t, 1H, J 8.3, $CH_{quinoxaline}$); 7.80 (t, 1H, J 8.3 Hz, $CH_{quinoxaline}$); 7.91 (d, 1H, J 8.3 Hz, $CH_{quinoxaline}$); 8.00 (d, 1H, J 8.3 Hz); 10.29 (s, 1H, $CH_{quinoxaline}$). The mass spectrum, *m*/*z* (I_{rel}, %), was: 263 [M^+] (73). $C_{17}H_{10}N_2O_4$.

2-(1-Phenyl-3-methyl-5-oxopyrazol-4-yliden)-1*H*-1,2-dihydroquinoxaline (IV). Compound I (0.130 g, 1.0 mmol) and pyrazolone (0.250 g, 1.44 mmol) were held for 48 h at 20 – 25°C in 1 ml of DMSO in the presence of 0.1 ml of HCl. The resulting precipitate was collected by filtration and washed with cold ethanol. The yield was 0.110 g (36%). The melting temperature was 158 – 160°C.

The PMR spectrum (DMSO-d_6), δ, ppm, was: 2.60 (s, 3H, CH_3), 7.12 – 7.17 (m, 1H, CH_{arom}), 7.36 – 7.41 (s, 2H, CH_{arom}), 7.54 – 7.60 (m, 1H, $CH_{quinoxaline}$), 7.71 – 7.76 (m, 1H, $CH_{quinoxaline}$), 7.84 – 7.87 (m, 1H, $CH_{quinoxaline}$), 7.91 – 7.94 (m, 1H, $CH_{quinoxaline}$), 8.01 – 8.04 (m, 2H, CH_{arom}), 9.14 (broad s., 1H, CH $CH_{quinoxaline}$). The mass spectrum, *m*/*z* (I_{rel}, %), was: 302 [M^+] (100). $C_{18}H_{14}N_4O_2$.

2-(1,3-Dimethyl-2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimid-5-yliden)-1*H*-1,2-dihydroquiloxaline (V). Compound I (0.130 g, 1.0 mmol) and 1,3-dimethylbarbituric acid (0.156 g, 1.0 mmol) were held in 1 ml of DMSO in the presence of 0.05 ml of H_2O for 95 – 100 h at 20 – 25°C. The precipitate was collected by filtration, washed with 5 ml of water, and dried. The yield was 0.085 g (30%). The melting temperature was >250°C. The PMR spectrum (DMSO-d_6), δ, ppm, was: 3.33 (s, 6H, 2 × CH_3); 7.65 – 7.70 (m, 1H, $CH_{quinoxaline}$); 7.78 – 7.85 (m, 1H, $CH_{quinoxaline}$); 7.95 – 7.97 (m, 1H, $CH_{quinoxaline}$); 8.02 – 8.06 (m, 1H, $CH_{quinoxaline}$); 10.57 (s, 1H, $CH_{quinoxaline}$); 16.27 (broad s, 1H, NH). The mass spectrum, *m*/*z* (I_{rel}, %), was: 284 [M^+] (100). $C_{14}H_{12}N_4O_3$.

2-(2,4-Dihydroxyphenyl)quinoxaline (VI). Compound I (0.130 g, 1.0 mmol) and resorcinol (0.135 g, 1.2 mmol) in 5 ml of ethanol were boiled for 5 min in the presence of 0.2 ml of concentrated HCl. The reaction mix was diluted 1:1 with water and cooled to a tempo 15 – 20°C. The precipitate of VI was collected by filtration. The yield was 0.055 g (25%). The melting temperature was >250°C. The PMR spectrum (DMSO-d_6), δ, ppm, was: 6.35 (d, 1H, J 2.8 Hz, CH_{arom}); 6.42 (dd, 1H, J 8.8, J 2.8 Hz, CH_{arom}); 7.68 – 7.74 (m, 1H, $CH_{quinoxaline}$); 7.76 – 7.82 (m, 1H, $CH_{quinoxaline}$); 7.97 – 7.99 (m, 1H, $CH_{quinoxaline}$); 8.00 – 8.03 (m, 1H, $CH_{quinoxaline}$); 8.07 (d, 1H, J 8.8 Hz, CH_{arom}); 9.55 (s, 1H, $CH_{quinoxaline}$); 9.88 (s, 1H, OH), 13.36 (broad s, 1H, OH). The mass spectrum, *m*/*z* (I_{rel}, %), was: 238 [M^+] (100). $C_{14}H_{10}N_2O_2$.

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